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RESEARCH ARTICLE

Observational study to compare antithrombin and thrombomodulin for disseminated intravascular coagulation

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Abstract *Background* There have been no studies comparing the effects of antithrombin (AT-III) and recombinant human soluble thrombomodulin (rhs-TM) on outcomes in patients with disseminated intravascular coagulation (DIC) associated with infectious diseases. *Objective* The aim of this observational study is to compare AT-III and rhs-TM in terms of outcomes such as mortality, length of hospitalization, and medical costs in patients with DIC associated with infectious diseases based on a Japanese administrative database. *Setting* A total of 7,535 patients with DIC associated with infectious diseases in 886 hospitals from 2010 to 2012 in Japan. *Methods* We collected patients' data from the administrative database to compare clinical and medical economic outcomes of patients with DIC. Patients were divided into two groups according to treatment of DIC: AT-III ($n = 3{,}601$) and rhs-TM ($n = 3{,}934$). *Main outcomes measure* In-hospital mortality (within 14 days, within 28 days, and overall mortality), length of stay (LOS), and medical costs during hospitalization. *Results* Multilevel logistic regression analysis showed that there were no significant differences with regard to in-hospital mortality between AT-III and rhs-TM within 14 days (odds ratio (OR) of rhs-TM 0.97, 95 % confidence interval (CI) 0.85–1.11, $p = 0.744$), within 28 days (OR 1.00, 95 % CI 0.89–1.13, $p = 0.919$), and overall (OR 0.95, 95 % CI 0.85–1.07, $p = 0.470$). However, multilevel linear regression analysis revealed that use of rhs-TM significantly decreased LOS and medical costs during hospitalization. The coefficient for LOS was -2.92 days (95 % CI -4.79 to -1.04 days; $p = 0.002$) whereas that for medical costs during hospitalization was -798.3 Euro (95 % CI $-1{,}515.7$ to -81.0 Euro; $p = 0.029$). *Conclusion* This study demonstrated no significant difference in in-hospital mortality between AT-III and rhs-TM. However, use of rhs-TM was significantly associated with decreased LOS and medical costs during hospitalization in patients with DIC associated with infectious diseases.

Keywords Antithrombin · Database · Disseminated intravascular coagulation · Healthcare costs · Length of stay · Mortality · Thrombomodulin

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Impact of findings on clinical practice

- There are no significant differences with regard to in-hospital mortality between antithrombin and recombinant human soluble thrombomodulin (rhs-TM) in patients with disseminated intravascular coagulation (DIC) associated with infectious diseases.
- Compared with AT-III, use of rhs-TM significantly decreased length of stay and medical costs during hospitalization of patients with DIC.

Introduction

Disseminated intravascular coagulation is a complicated and dynamic hemostatic disorder, and has been considered to reflect a simple excess production of fibrin together with consumption bleeding in the small vessels, which results in the activation of the coagulation system [1, 2]. This critical condition is frequently associated with infectious diseases including septic shock, and requires an accurate diagnosis and prompt treatment, including therapy for DIC and underlying diseases, all of which are important to increase survival rates and improve the prognosis for patients [1–3]. Some previous studies have showed that patients with DIC still have high mortality rates, so DIC has been recognized as a life-threatening condition all over the world [4–6].

Although the current management of DIC is primarily focused on treating any associated underlying diseases, clinical practice guidelines have pointed out that anticoagulant therapies are also required for patients with DIC [7]. Drugs such as heparin, protease inhibitors, and AT-III, are used as anticoagulant therapies for patients with DIC associated with infectious diseases in Japan [7–9]. Of these, AT-III, a single stranded glycoprotein secreted by hepatocytes and vascular endothelial cells, in particular has been known to contribute to the anti-inflammatory response as well as to anticoagulation. Some previous reports suggest that administration of AT-III, especially high-dose administration, was effective for patients with DIC associated with infectious diseases, so that AT-III has been highly recommended compared with other drugs in clinical practice guidelines for DIC [9, 10]. A recent nationwide database study also demonstrated that AT-III administration was associated with a reduction of 28-day mortality in patients with severe pneumonia and sepsis-associated DIC in Japan [11]. AT-III is therefore recognized as a beneficial drug for the treatment for DIC.

Recombinant human soluble thrombomodulin (rhs-TM), which exerts an anticoagulant effect mainly via the activation of protein C and leads to neutralization of inflammatory mediators and suppression of leukocyte-endothelial interaction, was approved for clinical use in 2008 in Japan [12]. This drug is a novel biological agent that provides a new treatment option for DIC, and some recent reports suggests that rhs-TM has contributed to an improved prognosis for patients with DIC associated with infectious diseases including sepsis [13–15]. Ogawa et al. [13] reported that rhs-TM may have a significant beneficial effect on respiratory dysfunction in patients with sepsis-induced DIC, while Saito et al. [14] also showed that administration of rhs-TM improved DIC resolution rate and alleviated bleeding symptoms compared with heparin. Current clinical practice guidelines have not assigned the recommendation for rhs-TM because of a lack of evidence to support its efficacy for the treatment for DIC. However, use of rhs-TM is expected to be beneficial and may replace traditional management of patients with DIC in Japan.

However, no studies have compared the effects of AT-III and rhs-TM on outcomes in patients with DIC associated with infectious diseases. In particular, no comparison exists in direct outcomes such as mortality, length of hospitalization, and medical costs between these treatments. Confirmation of the effects of these treatments would be useful for further studies about DIC, which would in turn have significant implications for treatments for patients with DIC.

Aim of the study

To retrospectively compare the clinical and economic outcomes of patients with DIC associated with infectious diseases after treatment with AT-III and rhs-TM.

Ethical approval

The research protocol of the study was approved by the ethics committee of medical care and research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Methods

Administrative database associated with the DPC system

We used a national administrative database developed for Japanese case-mix projects based on the Diagnosis Procedure Combination (DPC) system. The Japanese healthcare system has severe financial problems because of the expense of new medical technology, a rapidly aging society, and extended patient hospitalizations [16–20]. To address these issues, the Ministry of Health, Welfare and Labour and its affiliated research institute have begun investigating whether the Japanese case-mix classification system can be used to standardize medical profiling and payment [16–20]. Because of this, Japanese case-mix projects based on the DPC system were introduced to 82 academic hospitals (the National Cancer Center, the National Cardiovascular Center, and 80 university hospitals) in 2003 [16–20].

The DPC is a case-mix patient classification system linked with an incentive payment system which is similar to the diagnosis-related groups and prospective payments system in the United States or the Australia Medicare

program. In addition, all hospitals can participate in this project at any time [21]. Reimbursement from health insurance using the DPC system is common practice in Japan, and the number of DPC-participating hospitals has increased. Many hospitals involved are dispersed throughout Japan and play leading roles in providing acute care medicine, advancing medical research, and educating students and medical residents [16–20].

This system collects important data during hospitalization in addition to the characteristics of the unique reimbursement system. Each patient's financial data, claim information, and discharge summary, which includes principal diagnosis, complications, and comorbidities during hospitalization, are thoroughly recorded in the administrative database of the DPC system. These data are coded using the International Classification of Diseases and Injuries, 10th Revision (ICD-10) code. This administrative database also contains comprehensive medical information, including all interventional or surgical procedures, type and number of drugs and devices that have been indexed in the original Japanese code. The Ministry of Health, Welfare and Labour of Japan assigns these codes [16–20]. The date and amount of care delivered each day are also recorded in the DPC administrative database [16–20].

Enormous amounts of data on inpatients have been collected from DPC-participating hospitals annually, covering approximately 55 % of total inpatient hospitalizations, according to a report from the Ministry of Health, Welfare and Labour of Japan [22]. The DPC research group has conducted the study including the analysis on the effect or time trend of medical treatments as well as research with respect to medical economics or compliance with guidelines in DPC-participating hospitals. DPC-participating hospitals send all the anonymized data to the DPC research group, which in turn sends it to the server in our department [19]. The use of DPC data was permitted by all institutions and hospitals that provided detailed data.

Study setting

Information from 34,711 patients with DIC was collected using the DPC administrative database between fiscal years 2010 and 2012. We selected patients with DIC associated with infectious disease for this study because much previous research has focused the efficacy of AT-III or rhs-TM in patients with infectious diseases. We excluded 20,387 DIC patients with other underlying diseases. We also excluded 4,369 patients treated with neither AT-III nor rhs-TM, and 2,420 treated with both AT-III and rhs-TM. This left 7,535 patients with DIC associated with infectious disease for analysis in this study. These patients had been referred to 886 DPC participating hospitals (83 academic and 803 community hospitals). For the present analysis, patients were divided into two groups according to the single use of drugs for DIC associated with infectious diseases: AT-III group ($n = 3{,}601$) and rhs-TM group ($n = 3{,}934$; Fig. 1).

Study variables

Study variables included underlying diseases, age, sex, comorbid conditions, use of ambulance transportation, intensive care unit (ICU), and drugs for infectious diseases (antimicrobial, antifungal, and antiviral drugs), supportive care (central venous catheterization, vasopressor, artificial ventilation, and continuous hemodiafiltration), transfusion (platelet concentrates and fresh-frozen plasma), and other anticoagulant drugs (heparin and protease inhibitor), hospital type, size and region, and the proportion of hospitals with emergency centers.

We listed and classified the underlying diseases in the study sample. Age was stratified as follows: younger than 60, 60–79, and 80 years or older, as previously reported [23]. The severity of chronic comorbid conditions was assessed using the Charlson comorbidity index (CCI), which is widely used for recording comorbidities and has been validated in various studies [17–20]. The CCI score was calculated for each patient as in previous studies, where the association between the CCI and ICD-10 code has been demonstrated [17–20]. The CCI score was expressed as the score of all comorbid conditions and was initially evaluated as a continuous variable. However, categorical variables defining four categories of severity of chronic comorbid conditions were created to simplify the presentation of the results: 0, none; 1, mild; 2, moderate; and 3 or more, severe [17–20]. Regarding the treatment of patients, we referred to the clinical practice guidelines for DIC and infectious diseases [7, 24].

Hospital type was classified as academic or community [17–20]. Hospital size was categorized into three groups according to the number of hospital beds: small (<200 beds), medium (200–600 beds), and large (>600 beds) [18–20]. Hospital region was divided into two categories: urban and rural. We defined an urban region as a prefecture that has a degree of population concentration of 50 % or above, and a rural region as a prefecture that has a degree of population concentration of less than 50 %, as reported previously [25].

Main measure outcomes and statistical analysis

The main measure of interest in this investigation was to compare outcomes between AT-III and rhs-TM for patients with DIC associated with infectious diseases. Outcome

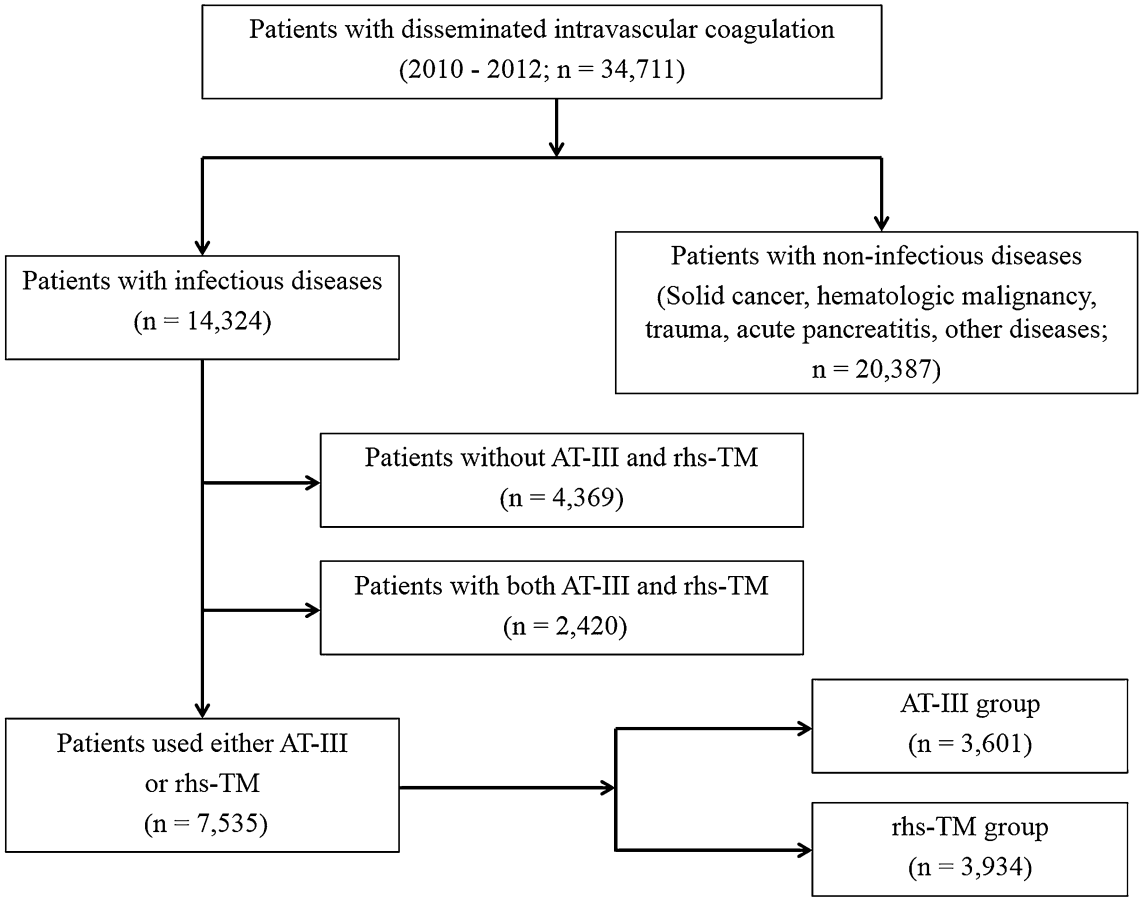

Fig. 1 Patient selection and classification from the administrative database (AT-III: antithrombin. rhs-TM: recombinant human soluble thrombomodulin)

variables were in-hospital mortality, length of stay (LOS), and medical costs during hospitalization. We defined medical costs during hospitalization as the direct cost of patients with DIC, and assumed an exchange rate of 140 Japanese Yen per Euro in this study (March 2014). These data have been recorded in the uniform format within the DPC system, to enable comparison between patients or hospitals. We used the Chi squared test for categorical data, and the Student's t test for continuous variables. In addition, we used simple and multilevel logistic regression models to estimate the odds ratios and their 95 % confidence intervals for in-hospital mortality within 14 and 28 days, and overall, to account for the clustering of patients within hospitals. The data of patient characteristics, such as underlying diseases, age, sex, chronic comorbid conditions, use of ambulance transportation and ICU, drugs for infectious diseases, supportive care, transfusion, and other anticoagulant drugs as well as hospital characteristics were considered as potential confounders and included in the logistic regression model. In additional analyses, multilevel linear regression models were used to identify the difference between AT-III and rhs-TM for DIC patients in terms of LOS and medical costs during hospitalization.

All statistical analyses were performed using the STATA statistical software package version 11.0 (Stata Corporation, College Station, TX, USA). A value of $p < 0.05$ was considered significant.

Results

A total of 7,535 patients with DIC associated with infectious diseases were identified for this study, comprising 3,601 patients treated with AT-III and 3,934 treated with rhs-TM.

The clinical characteristics and presentations of patients and hospitals are shown in Table 1. rhs-TM was used significantly more often than AT-III in patients with septic shock as the underlying disease ($p < 0.001$). There were no statistical differences with regard to age and comorbid

Table 1 Characteristics of patients and hospitals based on a national administrative database

	Overall (n = 7,535)	AT-III group (n = 3,601)	rhs-TM group (n = 3,934)	p value
Patient characteristics				
Underlying diseases (%)				
Septic shock	19.4	18.1	20.5	<0.001
Respiratory infections	30.1	29.9	30.2	
Digestive tract infections	17.7	19.2	16.4	
Urinary tract infections	12.1	9.4	14.6	
Others	20.7	23.4	18.3	
Mean age (years)	73.3	73.2	73.5	0.341
Age categories (%)				
Less than 60 years	13.5	14.3	12.7	0.066
60–79 years	44.4	43.3	45.5	
80 years or more	42.1	42.4	41.8	
Sex (%)				
Male	44.4	42.1	46.4	<0.001
Female	55.6	57.9	53.6	
Comorbid conditions (%)				
None (CCI;0)	43.0	41.7	44.2	0.067
Mild (CCI;1)	26.7	27.2	26.1	
Moderate (CCI;2)	16.4	16.3	16.5	
Severe (CCI;3 or more)	13.9	14.8	13.2	
Use of ambulance (%)	50.5	51.7	49.3	0.044
Use of intensive care unit (%)	17.8	19.6	16.2	<0.001
Drugs for infectious diseases (%)				
Antimicrobial drugs	97.8	97.4	98.2	0.020
Antifungal drugs	4.8	6.1	3.6	<0.001
Antiviral drugs	5.3	5.8	4.7	0.116
Supportive care (%)				
Central venous catheterization	60.1	67.0	53.7	<0.001
Vasopressor	57.1	60.4	54.1	<0.001
Artificial ventilation	34.4	37.2	31.9	<0.001
Continuous hemodiafiltration	3.5	3.3	2.2	0.028
Transfusion (%)				
Platelet concentrates	23.1	25.9	20.6	<0.001
Fresh-frozen plasma	18.7	25.5	12.4	<0.001
Other anticoagulant drugs (%)				
Heparin	31.0	43.1	20.1	<0.001
Protease inhibitor	8.8	11.9	6.1	<0.001
Hospital characteristics				
Hospital type (%)				
Community hospitals	83.7	81.9	85.3	<0.001
Academic hospitals	16.3	18.1	14.7	
Hospital size (%)				
Small sized hospitals	5.4	5.5	5.3	<0.001
Medium sized hospitals	63.8	66.8	60.6	
Large sized hospitals	30.8	27.7	34.1	
Hospital region (%)				
Rural region	37.2	39.6	35.1	<0.001
Urban region	62.8	60.4	64.9	

Table 1 continued

	Overall ($n = 7,535$)	AT-III group ($n = 3,601$)	rhs-TM group ($n = 3,934$)	p value
Emergency center (%)				
Without emergency center	60.9	57.1	64.4	<0.001
With emergency center	39.1	42.9	35.6	

AT-III antithrombin

rhs-TM recombinant human soluble thrombomodulin

CCI charlson comorbidity index

Table 2 Comparisons of in-hospital mortality, mean length of stay and medical costs between groups

	Overall ($n = 7,535$)	AT-III group ($n = 3,601$)	rhs-TM group ($n = 3,934$)	p value
In-hospital mortality (%)				
Mortality within 14 days	17.1	17.4	16.8	0.539
Mortality within 28 days	27.4	28.1	26.8	0.211
Overall mortality	41.0	43.5	38.6	<0.001
Mean length of stay (days)	36.9	40.3	33.8	<0.001
Mean medical costs (Euro)	18,062.4	19,940.8	16,343.0	<0.001

conditions between groups. The AT-III group had a significantly higher proportion of female patients compared with the rhs-TM group ($p < 0.001$). In addition, there was a higher frequency of supportive care and transfusion in the AT-III group than the rhs-TM group. Heparin was also more likely to be used in the AT-III than the rhs-TM group (42.1 vs. 20.1 %; $p < 0.001$). Regarding hospital characteristics, academic or emergency center hospitals were more likely in the AT-III group, while large-sized hospitals or hospitals in urban regions were more likely in the rhs-TM group ($p < 0.001$).

Comparisons of patient outcomes between groups are presented in Table 2. In-hospital mortality within 14 and 28 days was lower in the rhs-TM group than the AT-III group, but the difference was not significant for either (17.4 vs. 16.8 %; $p = 0.539$ and 28.1 vs. 26.8 %; $p = 0.211$, respectively). However, a significant difference between groups was observed in overall mortality (43.5 vs. 38.6 %; $p < 0.001$). Mean LOS was significantly shorter in the rhs-TM group (40.3 vs. 33.8 days; $p < 0.001$). In addition, mean medical costs during hospitalization were statistically lower in the rhs-TM group than in the AT-III group (19,940.8 vs. 16,343.0 Euro; $p < 0.001$).

The logistic regression analysis for in-hospital mortality is shown in Table 3. Simple logistic regression showed that the rhs-TM group had a decrease in overall mortality compared with the AT-III group (OR 0.81, 95 % CI 0.74–0.89; $p < 0.001$). However, after adjustment for patients' characteristics and hospital status, no significant association was observed for overall mortality (OR 0.95, 95 % CI 0.85–1.07; $p = 0.470$). Multilevel logistic regression also showed that there were no significant differences with regard to in-hospital mortality within 14 and 28 days (within 14 days: OR 0.97, 95 % CI 0.85–1.11; $p = 0.744$; and within 28 days: OR 1.00, 95 % CI 0.89–1.13; $p = 0.919$, respectively).

However, there was a consistently significant association between treatments and LOS after adjustment for potentially confounding clinical variables. Multilevel regression analysis showed that use of rhs-TM was significantly associated with decreasing LOS in patients with DIC. The coefficient was −2.74 days (95 % CI −4.63 to −0.85 days; $p = 0.005$). Regarding medical costs during hospitalization, it was confirmed that use of rhs-TM was significantly associated with decreasing medical costs in patients with DIC. The coefficient was −826.7 Euro (95 % CI −1,607.2 to −46.1 Euro; $p = 0.038$; Table 3).

Discussion

Using a national administrative database, we conducted this study to compare the effects of AT-III and rhs-TM on outcomes in patients with DIC associated with infectious diseases. We found that use of rhs-TM was associated with decreased LOS and medical costs during hospitalization.

Although the reason for these findings is not clear, several factors may be involved. First, some reports suggest that rhs-TM could rapidly decrease sepsis-related organ failure assessment or DIC score compared with control groups [26, 27]. Yamakawa et al. [28] also reported an association between use of rhs-TM and an increase in ICU-

Table 3 Simple and multilevel analysis for in-hospital mortality, mean length of stay and medical costs of patients

	Simple logistic regression			Multilevel logistic regression		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
Mortality within 14 days						
AT-III group	1.00			1.00		
rhs-TM group	0.96	0.85–1.08	0.539	0.97	0.85–1.11	0.744
Mortality within 28 days						
AT-III group	1.00			1.00		
rhs-TM group	0.93	0.84–1.03	0.211	1.00	0.89–1.13	0.919
Overall mortality						
AT-III group	1.00			1.00		
rhs-TM group	0.81	0.74–0.89	**<0.001**	0.95	0.85–1.07	0.470
	Simple linear regression			Multilevel linear regression		
	Coefficient	95 % CI	*p* value	Coefficient	95 % CI	*p* value
Length of stay (*days*)						
AT-III group	Reference			Reference		
rhs-TM group	−6.48	−8.29 to −4.68	**<0.001**	−2.92	−4.79 to −1.04	**0.002**
Medical costs (*Euro*)						
AT-III group	Reference			Reference		
rhs-TM group	−3,597.7	−4,359.8 to −2,835.6	**<0.001**	−798.3	−1,515.7 to −81.0	**0.029**

Odds ratios and coefficient adjusted for patient characteristics (underlying diseases, age, sex, chronic comorbid conditions, use of ambulance and intensive care unit, drugs for infectious diseases, supportive care, transfusion and other anticoagulant drugs) and hospital characteristics (hospital type, size, region and presence of emergency center)

Bold value indicates statistically significant values ($p < 0.05$)

free days, ventilator-free days, and vasopressor-free days. It is reasonable to suppose that faster recovery enables a reduction in LOS or medical costs during hospitalization. Second, both rhs-TM and AT-III are very expensive drugs. However, in the case of AT-III, some clinical studies have reported that there is no resolution of DIC or increase in survival time unless a high dose is used [9, 10, 29, 30]. In addition, several studies suggest that heparin was frequently used with AT-III as a concomitant therapy during treatments for DIC in Japan [10, 31]. Indeed, the frequency of use of heparin was significantly higher in patients treated with AT-III in our study. Furthermore, there was a higher frequency of supportive care or transfusion in the AT-III group, suggesting that there were more patients with severe disease in the AT-III group than the rhs-TM group. Therefore, the efficacy of rhs-TM in terms of rapid resolution of DIC, as well as characteristics of AT-III such as the need for high doses or concomitant drug therapy or patient's condition may have influenced LOS and medical costs during hospitalization in patients with DIC associated with infectious diseases.

However, no statistical differences were seen in in-hospital mortality within 14 or within 28 days in this study. In addition, the risk of death or overall hospitalization was the same with AT-III and rhs-TM, even after adjustment for patient or hospital characteristics. While many studies have focused on the efficacy of AT-III or rhs-TM for patients with DIC associated with infectious diseases [9–15], no studies exist to compare the outcomes between AT-III and rhs-TM. Recent studies showed the predominance of rhs-TM versus other treatments for sepsis-induced DIC. Yamakawa and colleagues compared the patient outcome between rhs-TM and a control group including the administration of AT-III, and reported that use of rhs-TM was significantly associated with reduced in-hospital mortality (hazard ratio 0.45, 95 % CI 0.26–0.77; $p = 0.013$) [28]. Kato et al. [26] reported that use of rhs-TM was associated with a significantly higher survival rate of patients with DIC compared with the control group. These studies did show an advantage of rhs-TM for patients with DIC associated with infectious diseases. However, they only compared rhs-TM with all treatments that did not include rhs-TM for patients with DIC, and as such did not directly compare AT-III and rhs-TM. Therefore, prospective or randomized studies are needed to confirm the efficacy of rhs-TM compared with AT-III for patients with DIC associated with infectious diseases.

The clinical data used represent a major strength of the current study. One of the benefits of the national database is that it enables evaluation of a large number of hospitals

in an unbiased manner, because our investigation involved a nationally representative sample of patients with DIC associated with infectious diseases in a community setting [16–20]. In addition, detailed medical data such as all procedures, medications, and devices have been extensively coded with original Japanese payment codes [16–20]. These data are recorded on a daily basis for each patient [16–20]. Therefore, this administrative database also enables interested parties to evaluate the clinical outcomes with individual detailed medical treatments.

Some potential limitations of this study also warrant mention. First, the data were obtained from only DPC-participating hospitals, which may have introduced selection bias. Data from non-DPC-participating hospitals should also be analyzed to reduce the possible bias. Second, we could not comment on accurate dosages of AT-III or rhs-TM. The DPC database has data on type and number of drugs used for each patient. However, the dosage of AT-III and rhs-TM is determined by the patients' weight, and we did not have this information. Dosage, particularly that of AT-III, may influence outcomes in patients with DIC. Third, we could not investigate the severity of the infectious diseases associated with DIC in this study. According to some recent guidelines, severity of disease should be determined by the patients' condition or laboratory or image findings [32]. However, our administrative database has not included these data. A recent report suggests that the severity of underlying disease was the important factor for survival of patients with DIC [33]. Fourth, we could not identify the patients who had received treatment for DIC several times during the study period. Fifth, protease inhibitors were used significantly more often in the AT-III group in this study. We assumed that protease inhibitors were used in the treatment of DIC, as well as for acute pancreatitis. This drug is frequently used in patients with acute pancreatitis in Japan [34]. However, we could not identify the cases in which protease inhibitors were used in the treatment of DIC. Therefore, further clinical studies evaluating the efficacy of rhs-TM against AT-III for patients with DIC may be required, taking into account more detailed data.

Conclusion

In conclusion, we demonstrated no significant difference in in-hospital mortality between AT-III and rhs-TM in patients with DIC associated with infectious diseases. However, use of rhs-TM was associated with reduced LOS and medical costs during hospitalization. Further prospective studies are needed to compare the efficacy of rhs-TM with AT-III for patients with DIC associated with infectious diseases in the near future.

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Conflicts of interest None of the authors have any conflicts of interest to declare.

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